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A COMPREHENSIVE REVIEW OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS: MECHANISM, USES AND SAFETY

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Abstract:

One of the most Popular treatments for treating pain, inflammation and fever is non-steroidal anti-inflammatory drugs (NSAIDS). Cyclooxydenase (COX) enzyme inhibition, which results in decreased prostaglandin synthesis involved in Inflammatory pathways is the main mechanism by which their therapeutic benefits are mediated. The mechanism of action categorization pharmacokinetic characteristics, and clinical uses of NSAIDs are all covered in detail in this article. It emphasises how COX- 1 and Cox- 2 selectively effects safety and efficacy profiles. Pharmacokinetic elements that affect drug distribution in inflammatory tissues are highlighted including absorption common distribution metabolism and elimination. The article also describes their involvement in anti-piracies and anti-thrombotic therapy as well as common therapeutic use in musculoskeletal inflammatory and post-operative disorders. Despite its therapeutic advantages NSAIDs must be used carefully because of side effects such gastrointestinal discomfort common renal impairment and medication interactions. The goal of recent developments is to increase safety and efficacy by concentrating or innovative hybrid molecules and selective COX2 inhibitors. NSAIDs are still necessary in clinical practice overall but their usage necessities careful assessment of each patients unique characteristics and risk profile.

Keywords: *Metformin, Lactic Acidosis, Type 2 Diabetes Mellitus, Renal Failure, Adverse Drug Reaction*

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INTRODUCTION:

Nonsteroidal Anti – Inflammatory drugs:

NSAIDs are a diverse class of drugs that have antipyretic, anti-inflammatory, and analgesic effects. Some, like phenylbutazone, are so hazardous that they can only be used to treat long-term inflammatory diseases like rheumatoid arthritis. Other, less harmful substances, such as diclofenac, ketorolac, and paracetamol, are frequently used to relieve postoperative pain. Similar to aspirin, paracetamol possesses analgesic and antipyretic properties, however it has very little anti-inflammatory action. It is therefore categorically not an NSAID. It is a strong prostaglandin inhibitor, similar to aspirin, but its effects are mostly limited to the central nervous system.

The Cascade of Inflammation

A mixture of mediators (K+, H+, cytokines, etc.) produces a "sensitizing soup" when tissue is injured. This sets off a series of events:

1. Phospholipase A2 Activation: This enzyme releases arachidonic acid from phospholipids in cell membranes when it is stimulated by trauma or chemical mediators (bradykinin, angiotensin II).
2. The COX Pathway: Arachidonic acid is converted by cyclo-oxygenase (COX) enzymes into unstable endoperoxides (PGG2, PGH2), which then transform into:

- Nociceptors are sensitized by prostaglandins (PGE2, PGI2), which causes hyperalgesia, or an enhanced sensitivity to pain.
- Platelet aggregation is facilitated by thromboxanes (TXA).

3. The lipoxygenase (LOX) pathway: which transforms arachidonic acid into leukotrienes—mediators frequently linked to asthma and allergy reactions—is likewise impacted by certain NSAIDs [(1)].

Mechanisms of Action of NSAIDs

- Primary Action: By blocking COX enzymes, NSAIDs lessen pain by preventing the synthesis of inflammatory prostaglandins.
- Reversibility: While other NSAIDs bind to COX reversibly (temporarily), aspirin binds irreversibly (permanently).
- LOX route: While salicylates do not impede the lipoxygenase (LOX) route (leukotriene synthesis), certain medications, such as diclofenac and indomethacin, do.
- Central Effect: Rather than acting at the site of damage, paracetamol mainly acts in the Central Nervous System (CNS).
- Secondary Actions: G-protein signaling in cell membranes is disrupted or cytokines (IL-2, IL-6, TNF-α) are modulated by certain NSAIDs (such as oxicams).

Selectivity of COX-1 against COX-2

The COX enzyme, which defines a drug's impact and safety profile, is produced by the body in two primary forms:

- COX-1 (Constitutive): In charge of "house-keeping" (defending the kidneys and stomach lining). Side effects like ulcers result from inhibiting this.
- COX-2 (Induced): Generated especially when there is inflammation. Therapeutic comfort (reduced pain/fever) is obtained by inhibiting this.

- Drug Differentiation: Ibuprofen/Aspirin: Stronger COX-1 inhibitors (greater risk of upset stomach).
  - → Naproxen and diclofenac are balanced inhibitors.
  - → Nabumetone: Less likely to cause stomach ulcers as it is more selective for COX-2.

Onset Time:

Because NSAIDs work indirectly—that is, by preventing the synthesis of new molecules rather than blocking preexisting pain signals—they have a latent period of up to 40 minutes.

Non-Specificity:

Because the majority of NSAIDs decrease COX worldwide, they frequently damage both the injured location and healthy tissue, such as the stomach and kidneys [(1)].

History:

The Typical Biochemical Objective: The fact that chemically distinct medications, such as aspirin and ibuprofen, had the same effect perplexed scientists for decades. They all target the Arachidonic Acid Pathway, as we now know:

- The Trigger: Arachidonic acid is released by a broken cell membrane.
- The Enzyme: Cyclo-oxygenase (COX) is an enzyme that "chews" up that acid.

- The product: Prostaglandins, the biological "messengers" for pain, fever, and edema, are created when COX converts the acid.
- The Blockade: NSAIDs function similarly to a physical plug. They prevent the COX enzyme from producing those painkillers by sitting inside of it.

Categorization and Definition:

- Aspirin-like Drugs: Despite having differing chemical structures, medications including naproxen, phenacetin, and paracetamol are classified together because they have similar therapeutic benefits.
- The term "Nonsteroidal Anti-inflammatory Drugs" (NSAIDs) is used to differentiate them from glucocorticoids (steroids).
- Core Trio of Effects: They all act as anti-inflammatories (swelling/redness), antipyretics (fever), and analgesics (pain).

Functions of "Trio": They all consistently offer three primary advantages because they prevent prostaglandins:

- Analgesics: They increase your threshold for pain, particularly for joints and headaches.
- Antipyretic: They decrease fevers by resetting the hypothalamic "thermostat" of the body.
- Anti-inflammatory: They lessen fluid accumulation (swelling) and blood flow at the site of an injury.

The Timeline of Evolution: The shift from "nature's pharmacy" to precision chemistry can be seen in the history:

- Ancient Pharmacy: Salicin is found in willow and myrtle. Humans' digestive systems transformed the salicin into salicylic acid when they consumed or drank decoctions of these plants.
- The "Four Cardinal Signs" of inflammation, which are still taught in medical schools today, were identified by Celsus in AD 30.
    - Rubor (redness)
    - Calor (Heat)
    - Dolor (discomfort)
    - Tumor (Swelling)
- The "Aspirin" Shift: Since pure salicylic acid is an acid, it was quite painful on the stomach despite being effective. Chemists added a "acetyl" group to it in the late 1800s to create Acetylsalicylic Acid (Aspirin), which retained its therapeutic properties while being easier to swallow.

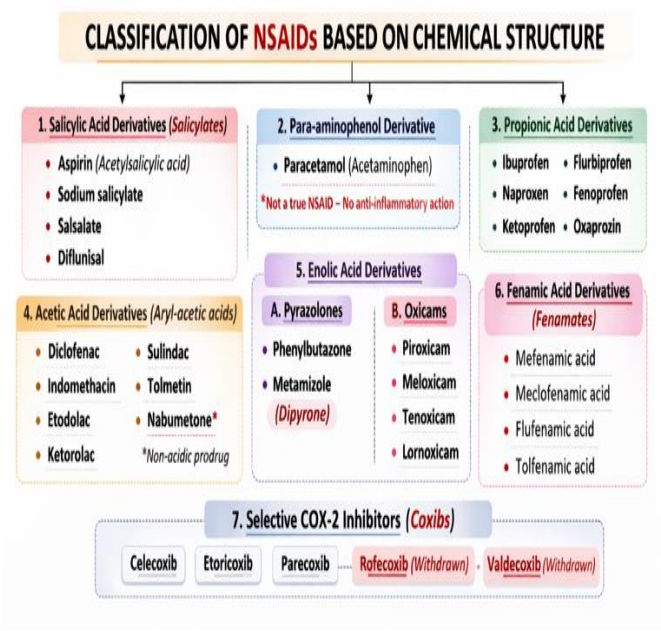
The Double Edged Swords (Side Effects): Not only are prostaglandins "bad" molecules, but they also aid in renal function and preserve the lining of the stomach.

- The Conflict: When an NSAID inhibits COX to relieve knee pain, it unintentionally inhibits COX in the stomach.
- The Conclusion: prolonged use may cause kidney problems or stomach ulcers. This "shared mechanism" explains why the warning labels on nearly all NSAIDs are identical.

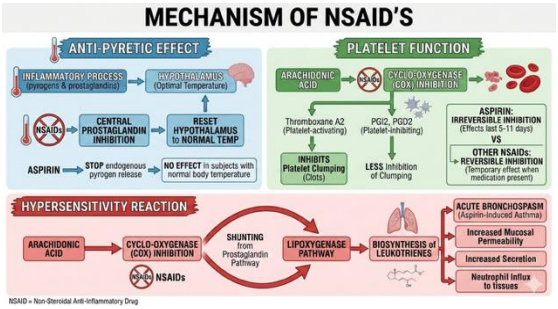
Clinical Characteristics and Adverse Reactions:

- Common Risks: Delayed labor, renal damage (in the event of an overdose), and upset stomach are common adverse effects.
- Anti-thrombotic Effect: Although "blood-thinning" was once thought to be a side effect, it is now a crucial therapeutic application for preventing clots.
- Universal Mechanism: Researchers concluded that for these various substances to have the same therapeutic effects, they must target a single metabolic pathway [2,3].

Classification:



Mechanism Of Action:



Pharmacokinetics:

Absorption:

With a few exceptions (such as celecoxib and diclofenac), NSAIDs have a high bioavailability (80–100%) and are often well absorbed after oral consumption. With the exception of some enolic acid derivatives (piroxicam, meloxicam, nabumetone) and some diaryl heterocyclic compounds (celecoxib, rofecoxib), their absorption is typically rapid, and peak plasma concentrations are typically seen within two to three hours. Consuming food may cause absorption to be delayed, but it seldom reduces systemic availability. While certain drugs, like dipyrone, nabumetone, sulindac, or etoricoxib, undergo a first-pass metabolism that produces the active substance, others, like diclofenac or aspirin, experience a large first-pass impact that considerably affects their bioavailability. NSAIDs seem to penetrate inflammatory tissues and joints very little when given topically, and detectable quantities in synovial fluid following certain topical therapies (such as diclofenac) appear to rely on systemic circulation and skin absorption.

Distribution:

The majority of NSAIDs have a 95–99% binding to plasma proteins, which may be saturable and could interfere with other medications that vie for the same binding sites. The pharmacological actions and adverse effects of NSAIDs are significantly influenced by the distribution pattern. The majority of chemicals reach central nervous system concentrations high enough to produce a central analgesic effect, although specific physicochemical properties, such as acidity, appear to influence their kinetics in inflammatory foci. Diclofenac, ibuprofen, ketoprofen, and lumiracoxib are examples of acidic medications (pKa 4-5) that appear to concentrate and persist in inflammatory tissue, such as the synovial fluid of inflammatory joints (reviewed in Brune and Patrignani). This buildup could result from a number of factors:

- Nonionic transport of these medications into the cell interior is facilitated by the local acidic milieu brought on by inflammation; once inside, drug ionization is produced by the increased intracellular pH. This process, known as ion trapping, raises the drug's intracellular concentration.
- Protein-bound and protein-unbound medications can enter the tissue due to alterations in the hemodynamics of the tissue during inflammation, such as increased regional blood flow and edema.
- Drugs with a high affinity for albumin are retained due to the high abundance of this protein in inflammatory tissues and synovial fluid.
- The extracellular pH is slightly acidic, which may decrease their binding to plasma proteins and raise the drug's free fraction.

- Acidic NSAIDs: In order to successfully reduce swelling, these medications target the low pH (acidity) of inflammatory tissue.

- Ion Trapping: This concentration induces "trapping" in the kidneys and stomach, which damages organs, but it also lasts longer than the drug stays in the blood.

- Non-Acidic Drugs: Instead of focusing on particular areas of the body, paracetamol and dipyrone disperse evenly throughout.

- The outcome is that non-acidic medications relieve pain but are unable to combat inflammation because they do not "pool" in inflammatory sites.

Elimination:

The majority of NSAIDs are eliminated from plasma via renal excretion of their metabolites after hepatic biotransformation. With the exception of salicylic acid and indomethacin, most active medications have very little renal excretion (Table 1.5). Nearly all of them have variable degrees of biliary excretion and reabsorption (enterohepatic circulation), which appears to be a factor in NSAID enteropathy. Some have active metabolites, such as nabumetone and sulindac. While some NSAIDs undergo just phase II processes, others undergo phase I (oxidation, hydroxylation, and demethylation) and phase II (glucuronidation, other conjugations) modes of metabolism. The half-lives of the medications in the

NSAID family range greatly, from 20 to 60 hours for oxicams to 1 to 4 hours for ibuprofen, diclofenac, or acetaminophen. The half-life of COX-2-selective medications is intermediate.

According to some authors, the short half-life of acidic compounds is advantageous because it allows for the recovery of COX-2 activity in endothelial cells at the end of each dosing interval. At the same time, the accumulated drug continuously inhibits the analgesia caused by COX blockade in the inflammatory tissue. This argument might likewise be used for other organs and tissues where prostaglandin synthesis has a homeostatic effect. Changes in hepatic metabolism in the elderly result in decreased clearance of several NSAIDs. Furthermore, older patients may have larger quantities of unbound NSAIDs due to reduced plasma albumin levels. The increased vulnerability to gastrointestinal issues seen in elderly patients can be explained by these raised NSAID concentrations in addition to compromised stomach mucosal defenses [5,6].

Therapeutic Uses:

NSAID'S are commonly used to treat acute and chronic conditions which includes pain and inflammation:

Arthritic and Inflammatory Disorders:

- Rheumatoid arthritis
- Osteoarthritis
- Ankylosing spondylitis
- Psoriatic arthritis
- Reactive arthritis
- Acute gout

Musculoskeletal Conditions:

- Muscle aches
- Low back pain
- Tennis elbow
- Traumatic injury
- Muscle stiffness

General Pain management:

- Mild to moderate pain due to inflammation and tissue injury
- Postoperative pain
- Dental pain
- Metastatic bone pain
- Renal colic
- Headache

Gynecological issues:

- Dysmenorrhea

Antipyretic Use:

- Fever
- Cold

Inflammation:

- Patient Variability: Each patient's response varies greatly; 40% of patients may not respond to one NSAID but respond to another.
- Timing: While anti-inflammatory effects may take up to three weeks, pain reduction peaks in one week.
- Rule: If no improvement is shown during these times, change your medicine.

Surgical Pain:

- Opioid Sparing: Using NSAIDs before to surgery can lessen post-operative pain and the need for opioids.
- Synergy: When used with paracetamol, it is frequently more effective.
- Caution: Little research has been done on risks such renal damage or surgical bleeding.

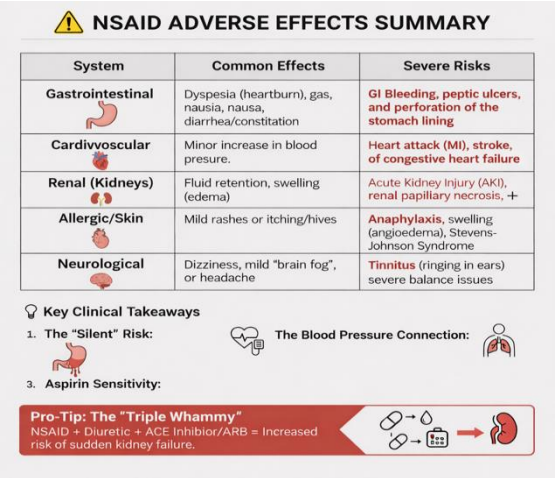
Anti-Coagulant (Aspirin):

- The only medication that permanently inhibits COX-1 is aspirin.
- Mechanism: Prevents platelets from adhering to one another by blocking thromboxane A2.
- Use: Prevents arterial thrombosis, heart attacks, and strokes.

Use of Dentistry:

- Preference: Because of its anti-inflammatory properties, NSAIDs are better than paracetamol for dental extractions.
- Pre-op Use: Taking them before to orthodontic procedures may reduce the amount of time that healing pain lasts [7,8].

Adverse Effects:



Drug Interactions:

Category	Drug / Examples	Mechanism of Interaction	Clinical Effects / Risks
Antihypertensives	ACE'S, ARB'S , Calcium Channel Blockers, Diuretics	NSAIDs reduce natriuresis, increase salt and water retention, and lessen the effects of ACE inhibitors by inhibiting renal prostaglandin formation.	Spironolactone increases the risk of gastrointestinal bleeding; piroxicam, naproxen, indomethacin, and high-dose ibuprofen increase blood pressure; and senior people are more susceptible to acute renal injury.
Antithrombotics	Aspirin, Warfarin	Reduce the cardioprotective effect by competing with aspirin at COX-1; increase the risk of hemorrhage	GI hemorrhage; increased risk of myocardial infarction (ibuprofen + aspirin); and increased risk of bleeding while taking warfarin
Antidepressants	Sertraline, Fluoxetine, Paroxetine	Reduced platelet serotonin uptake impairs platelet aggregation; certain SSRIs block CYP2C9, which raises NSAID levels.	Increase in GI bleeding (synergistic effect); the relative risk for GI hemorrhage with SSRI alone is 2.6.
Alcohol	Chronic alcohol consumption	Additional harm to the stomach mucosa	2.7-fold increase in GI bleeding (ibuprofen + alcohol); Odds ratio 10.2 when both alcohol misuse and NSAIDs are present
Chemotherapy	Methotrexate	NSAIDs raise medication levels by reducing methotrexate's renal clearance.	Increase in risk of pancytopenia, renal failure, and bone marrow suppression
Herbal products	Ginkgo biloba	It shows its effect on platelet function.	Anecdotal evidence of bleeding, including intracerebral hemorrhage
Female Reproductive Health	HRT	Possible interaction with cardioprotective effects	Potential rise in the risk of myocardial infarction when combined

Table 1 [10,11]

Recent advancement in NSAID'S:

The cyclooxygenase (COX) enzymes, which include the COX-1 and COX-2 isoforms, are in charge of producing prostaglandins. Selective nonsteroidal anti-inflammatory medication (NSAID) dosing is necessary to control prostaglandins, which play important roles in the inflammatory process. Because they lessen pain and guard against illnesses linked to inflammation, selective COX-2 inhibitors have been among the most popular NSAIDs during the ongoing coronavirus 2019 pandemic. It is necessary to evaluate the mechanisms of action of both COX isoforms, especially COX-2, as mediators of inflammation within this framework. Furthermore, proinflammatory cytokines including interleukin (IL)-6, IL-1β, IL-8, and tumor necrosis factor-α

must be emphasized because they play a significant role in the elevation of the inflammatory response. Lead structures with greater selectivity and potency against inflammation with fewer side effects may be introduced through structural and functional investigations of selective COX-2 inhibitors within the active-site cavity of COXs. The biological activity of recently identified synthetic COX-2, dual COX-2/lipoxygenase, and COX-2/soluble epoxide hydrolase hybrid inhibitors is the main subject of this review, which is mostly based on the active themes of relevant US Food and Drug Administration-approved medications. When compared to the NSAIDs celecoxib, valdecoxib, and rofecoxib, these novel medicines may offer a number of benefits, including gastrointestinal protection, anti-inflammatory action, and a safer profile [(12)].

Evolution of NSAIDs: From Traditional Agents to Next-Generation Innovations

Generation / Era	Type of NSAIDs	Examples	Mechanism of Action	Advantages	Limitations / Issues
First Generation (1890s–1980s)	Traditional Non-Selective NSAIDs	Aspirin, Ibuprofen, Naproxen, Indomethacin, Diclofenac, Piroxicam	Non-selective inhibition of COX-1 & COX-2	• Effective analgesic, antipyretic & anti-inflammatory effects • Low cost	• GI irritation, ulcers; • Renal toxicity; • Platelet inhibition
Second Generation (1990s)	Preferential COX-2 Inhibitors	Meloxicam, Nimesulide, Etodolac	Greater inhibition of COX-2 than COX-1	• Reduced GI side effects	• CV & renal risks
Third Generation (Late 1990s–2000s)	Selective COX-2 Inhibitors (Coxibs)	Celecoxib, Rofecoxib (withdrawn), Valdecoxib (withdrawn), Etoricoxib	Selective COX-2 inhibition	• Less GI ulceration	• CV & renal risks
Fourth Generation (Recent Developments)	Dual-Action & Safer NSAIDs	NO-Donating NSAIDs Phosphatidylcholine NSAIDs, COX/LOX Dual Inhibitors	• COX inhibition + NO release or other protective mechanisms	• Reduced GI damage; • Better safety profile	• Still under research; • Long-term safety data limite
Next-Generation Innovations	Targeted & Personalized Approaches	Nanotech NSAIDs Topical Delivery Systems Biased COX Inhibitors	• Targeted delivery & selective modulation	• Improved efficacy; • Reduced systemic effects	• High cost; • Limited availability

CONCLUSION:

As NSAIDs block prostaglandin synthesis through cyclooxygenase enzymes, they are essential in the treatment of pain, inflammation, and fever. They are essential in clinical practice because of their efficacy in treating a variety of acute and chronic diseases. Non-selective COX enzyme inhibition, however, is a contributing factor to negative consequences, especially renal and gastrointestinal issues. NSAIDs' pharmacokinetic characteristics, such as their strong protein binding and dispersion in inflammatory tissues, have a major impact on how well they work. The necessity for customized therapy is further highlighted by patient response variability and the possibility of medication interactions. A significant development aimed at lowering toxicity without sacrificing efficacy is the creation of specific COX-2 inhibitors and more recent hybrid medications. Even with these advancements, prudent monitoring and sensible prescribing are still necessary to reduce dangers. In conclusion, NSAIDs are still useful therapeutic drugs, but using them safely requires weighing the advantages against any possible drawbacks.

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